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Extending the Spectrum of Distal Arthrogryposis

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We describe a mother and son with multiple, non-progressive, congenital contractures, camptodactyly and absent flexion creases, expressionless face, blepharophimosis, microstomia, and short stature. Although these cases share similarities with the autosomal-recessive Schwartz-Jampel and Marden-Walker syndromes, they have a different mode of inheritance and lack myotonia, one of the most characteristic findings of the Schwartz-Jampel syndrome. Our cases most closely resemble those previously reported as distal arthrogryposis type IIb, although in our patients the proximal joints are severely affected and extraocular involvement is absent. Hearing loss is present in one and cleft palate in the other of our patients; these findings were previously described in arthrogryposis syndromes other than type IIb. We suggest extending the spectrum of distal arthrogryposis to include these manifestations, since there appears to be significant overlap between the different syndromes. © 1996 Wiley-Liss, Inc.

KEY WORDS: distal arthrogryposis, absent flexion creases, blepharophimosis, dominant inheritance, expressionless face, short stature

INTRODUCTION

Recently we evaluated a mother and son because of multiple, non-progressive, congenital contractures, expressionless face with blepharophimosis, and microstomia and short stature.

CLINICAL REPORTS

Patient 1

C.W. was the first child of healthy, nonconsanguineous parents (Fig. 1); she has one healthy brother and her mother had three spontaneous miscarriages. After an uncomplicated pregnancy she was born to a 17-year-old mother and a 21-year-old father. Gestational age was reported as 32 weeks, birthweight was 2.3 kg (>90th centile; 50th centile for 34 weeks), length was 43 cm (50th centile), and OFC was 35 cm (>90th centile; 50th centile for 42 weeks). At birth "anomaly of feet and hands," arachnodactyly, and low hairline were noted. A lacunar skull was seen on radiographs. Flexion contractures of hips and knees, talipes equinovarus, Achilles tendon shortening, and ulnar deviation of the wrists were described at 3 months and subsequently required multiple operations. Bilateral hamstring releases were done at 3 years; at 4 years bilateral Achilles tendon lengthenings and at 6 years tendon transfer at the right elbow were performed. Severe kyphoscoliosis developed during adolescence and was treated by posterior spinal fusion of the thoracic vertebrae at 13 years. No muscle weakness or myotonia was noted at any time. Karyotype from blood lymphocytes showed a 46,XX pattern with no obvious abnormality and no evidence of aminoacidopathies was found on thin layer chromatography. As a child she had multiple ear infections and middle ear ventilatory tubes were placed. A moderate high frequency sensorineural hearing loss in the right ear and a moderate to severe mixed hearing loss in the left ear were recognized. Hearing aid therapy was initiated at 20 years. Spectacles for myopia have been used since age 7 years. Motor development was delayed with sitting at 11 months and cruising at 14–15 months. Social and language development appeared age-appropriate. The patient attended special education classes and graduated from high school.

At $22^{10}/_{12}$ years C.W. was seen for the first time in our clinic (Fig. 2). She presented 20 weeks pregnant for evaluation and counseling regarding her previously suspected Schwartz-Jampel syndrome. Head circumference was 57 cm, within 2 SD for age and sex; height was 145.9 cm (<3rd centile; 50th centile for $11\frac{1}{2}$ years); span was 136.2 cm; upper segment was 73.3 cm; and lower segment was 75.6 cm. Pregravid weight was

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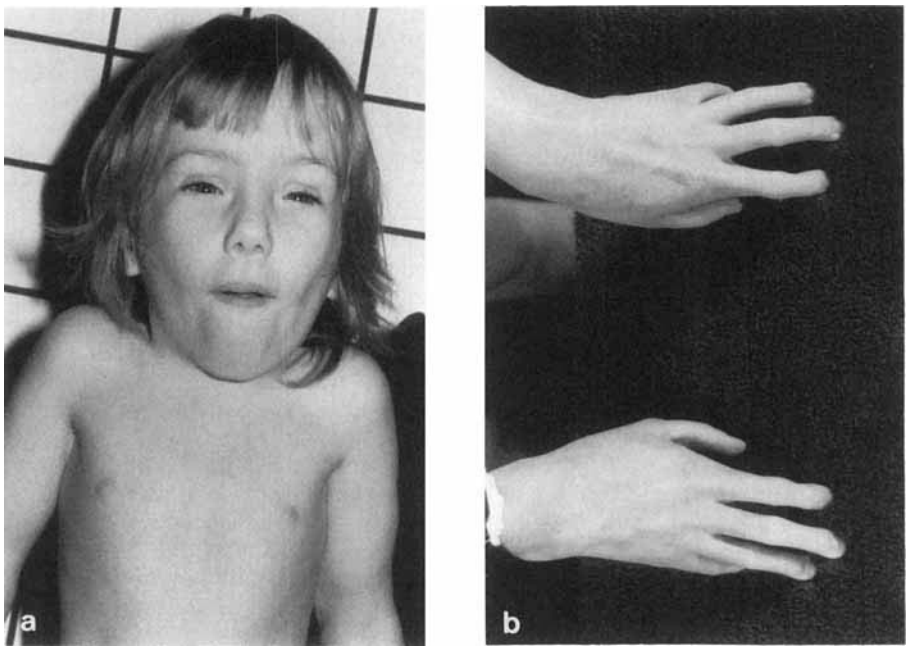

Fig. 1. **a:** Patient 1 at 5 8/12 years. Note expressionless face, blepharophimosis, microstomia, short neck. **b:** Hands of patient 1 at 23 years showing camptodactyly.

about 43 kg. She had a stiff gait but could arise rapidly from a sitting posture. The face appeared slightly mask-like, although she could smile in a limited manner. Blepharophimosis was obvious with palpebral fissures measuring 2.4 cm in length(<5th centile) and 0.9 cm in height. Extraocular movements were intact. Moderate limitation in opening of the small mouth was noted, but the lips were not pursed or puckered. Intercommisural distance of 42 mm was of average size for age 8–9 years. Ears were apparently low-set. The high palate showed a central midline groove. A relatively short neck had a limited range of motion. Increased AP diameter of the chest without pectus was seen. Heart sounds were normal. The skin had a tight, firm consis-

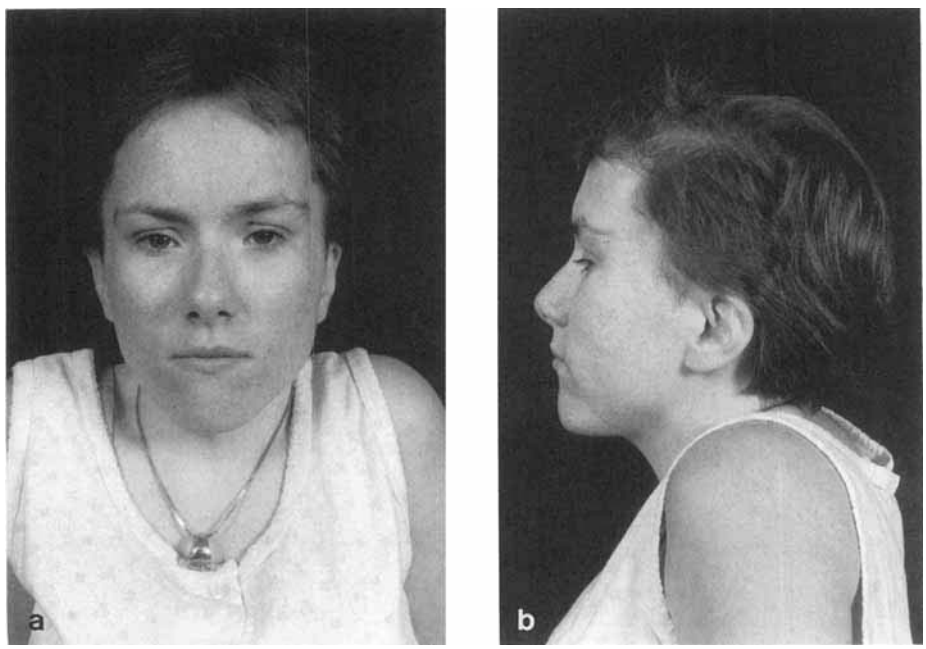

Fig. 2. **a,b:** Patient 1 at 23 years. Note expressionless face, blepharophimosis, microstomia, apparently low-set ears, and short neck.

tency, particularly over forearms and hands. Two palmar flexion creases were present bilaterally, and all digital flexion creases were hypoplastic or absent. Skeletal habitus was one of symmetric limbs that showed multiple contractures and general limitation in range of motion. The elbows were prominent and had full flexion but lacked about 40° of extension; pronation and supination were limited to a 30° arc. Broad and thick wrists were held in slight ulnar deviation. There was camptodactyly of all four fingers bilaterally and the thumbs had mild contractures as well. Range of motion was normal in the MP joints, but very limited in PIP and DIP joints. The patient was able to oppose the thumb to all four fingers and had a good grasp. There was limited range of motion in the hips, but full flexion and extension in the knees. The feet appeared short and extremely narrow with underriding first, fourth, and fifth toe bilaterally. Mild residual clubfeet with varus deformities of the hindfeet were noted. The ankles dorsiflexed to neutral. Muscles were somewhat firm but there was no clinical myotonia. Deep tendon reflexes were symmetric and equal.

The diagnosis of Schwartz-Jampel syndrome was suggested at another center as an explanation for her appearance with limited facial expression and multiple contractures. However, electromyography (EMG) and nerve conduction studies performed after the birth of her first child (patient 2) did not show evidence of myotonia or other abnormalities.

Patient 2

F.J. was the first child born to his 23-year-old mother (patient 1) and a 24-year-old father. The father was 194 cm (>97th centile) tall and had a history of strabismus and learning disability. On ultrasound examination at 34 weeks of gestation the fetus was reported to have "a low hairline on profile," apparently low-set ears, and mild limb shortness with abnormal ("gnarled") appearance of hands and feet. F.J. was delivered at 37 weeks gestational age via elective cesarean section due to maternal scoliosis. Apgar scores were 6 at 1 minute and 9 at 5 minutes, birthweight was 2.4 kg (25th centile), and was OFC 35 cm (90th centile). Multiple congenital anomalies were noted at birth, and his facial expression dramatically resembled that of the mother (see Figs. 1 and 3). The forehead was square and prominent with soft tissue folds vertically in midline, eyes were deeply set, nose was short with anteverted nostrils, ears were low-set, and mouth was small with limited opening and a cleft in soft and hard palate. Hirsutism involved arms and shins; the skin was of shiny appearance and doughy texture. Elbows were held in flexion, but could be extended fully. Ulnar deviation and flexion contractures of wrists and single palmar flexion creases were seen bilaterally. Fingers were long and stick-like with camptodactyly, minimal motion at IP joints, and hypoplastic joint creases. Flexion contractures of hips and knees as well as talipes equinovarus posture of feet were present. Delayed ossification of sternum, pelvis, femur, tibia, and calcaneus were noted on skeletal radiographs; there was no evidence of epiphyseal stippling. A small ASD closed spontaneously. Feeding difficulties required placement of a gastrostomy tube on the 23rd day of life and the patient received continuous nighttime feeds for more than 18 months. After recurrent bouts of otitis media bilateral myringotomy tubes

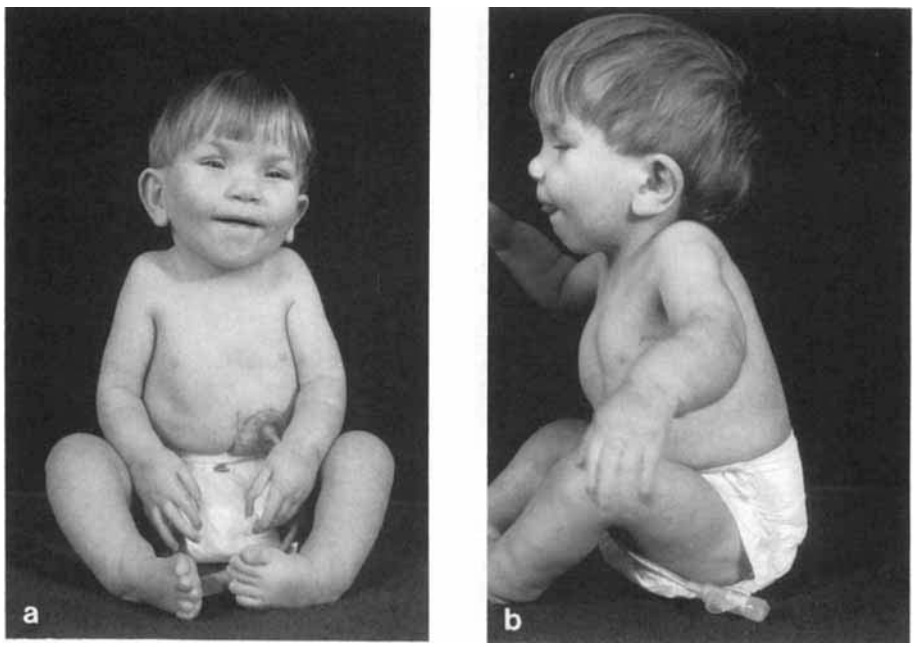

Fig. 3. **a,b:** Patient 2 at 17 months. Note expressionless face, blepharophimosis, microstomia, apparently low-set ears, short neck, and gastrostomy tube. Camptodactyly, talipes equinovarus and flexion contractures of hips and knees are shown.

were inserted at 14 months. Repair of the cleft palate was intended at that time, but could not be done because of multiple unsuccessful attempts of intubation, due to bony and soft tissue restriction allowing only limited mouth opening. At 17 months palatoplasty was performed (Fig. 3). The procedure was again complicated by restricted mouth opening and difficult intubation. The severe clubfoot deformities required surgical repair with posterior medial and lateral releases and subsequent bilateral talectomies. The patient was unable to walk prior to release of the clubfeet, but had pulled himself to stand since 12 months and his social and language development were age-appropriate. Myotonia was neither seen clinically nor in an EMG study. MRI of the brain was within normal limits as were tests for prenatal infections and light microscopy of a skin biopsy. High resolution chromosomes from blood lymphocytes showed a 46,XY pattern without obvious abnormality. A study for the Miller-Dieker syndrome, performed because of prominent soft tissue folds on the forehead, did not demonstrate a microdeletion.

On physical examination at 20 months his length was 71 cm(<3rd centile; 50th centile for 9 months), span was 60 cm, and weight was 7.9 kg (<3rd centile, 50th centile for 5 months). OFC measured 45.4 cm (<5th centile; 50th centile for 8 months). He was alert and smiled weakly on provocation, but most of the time his face appeared expressionless. Palpebral fissures were small, extraocular movements were intact, and the nose was short with a broad, blunt tip and slightly anteverted nostrils. Glabellar nevus flammeus was present and the skin in that area continued to be wrinkled and vertically folded. Apparently low-set ears, mild midface hypoplasia, long and broad philtrum and a small mouth measuring 2.6 cm (average size for age is 3.2 cm) intercommissurally were seen. There was good range of motion of the very short neck. The bell-shaped chest was narrow at the level of the axillary folds and broad at the lower ribs. No murmurs or clicks were noted on cardiac exam. The gastrostomy tube was still in place. Multiple contractures involving shoulders, elbows, wrists, and hips persisted. Both elbows had minimal pronation and supination, extension lacked about 40°, but flexion was full. Fingers appeared long and stick-like with persistent camptodactyly (palm 6.5 cm bilaterally, middle finger 4.5 and 4.7 cm left and right, respectively, all 75–97th centile for age). Hips had full flexion, but on extension 30° flexion contractures were seen bilaterally. Both knees showed 10° flexion contractures. No focal abnormalities were noted on neurological examination; muscle tone was normal, specifically it was not increased and there was no myotonia.

DISCUSSION

Patient 1 and her son, patient 2, have a syndrome of congenital joint contractures, expressionless face with blepharophimosis and microstomia, and short stature. The cases fulfill the definition of arthrogryposis multiplex congenita, also known as multiple congenital contractures, consisting of "multiple, non-progressive contractures in two or more body areas" [Stevenson et al., 1993, p 798 ff]. Several of the conditions associated with arthrogryposis can be ruled out, since our patients lack characteristic findings, for example, the typical limb positioning of amyoplasia, the pterygia of the multiple pterygium syndrome, and the unusual ear shape of contractural arachnodactyly. Lethal conditions such as the Pena-Shokeir syndrome are extremely unlikely to be present in cases reaching the age of reproduction. Other conditions associated with arthrogryposis show similarities with the described cases. The Schwartz-Jampel syndrome, also known as chondrodystrophic myotonia, is an autosomal recessive trait with mask-like face, narrow palpebral fissures, microstomia, micrognathia, myotonia, muscular hypertrophy, osteochondrodysplasia, and growth retardation. It was initially described by Catel [1951], and later by Schwartz and Jampel [1962]; since then about 40 cases have been reported [Edwards and Root, 1982]. Most patients show onset of signs in infancy [Farrell et al.,1987]. Myotonia on clinical examination or myotonic discharges on EMG are a characteristic finding, although their pathophysiology appears to be variable [Spaans et al., 1990] and some patients lack both [Moodley and Moosa, 1990]. Only one family with presumed Schwartz-Jampel syndrome has been reported involving several generations, with myotonia present in all three generations, the second generation also showing mild blepharophimosis and short neck, the third generation with face typical of Schwartz-Jampel syndrome and short stature; but none of these patients had joint contractures [Ferrannini et al., 1982]. Our cases differ from those described with typical Schwartz-Jampel syndrome because they lack myotonia and they have a dominant mode of inheritance.

Marden and Walker [1966] described a syndrome resembling the Schwartz-Jampel syndrome, but without myotonia. Joint contractures, fixed facial expression with blepharophimosis, failure to thrive, arachnodactyly, and kyphoscoliosis are seen in patients with this syndrome and are matched by our cases. However, the Marden-Walker syndrome is a recessive trait and therefore does not fit the inheritance pattern in our cases.

The Freeman-Sheldon syndrome is an autosomal dominant syndrome characterized by a mask-like facies with a small mouth giving a "whistling" appearance, blepharophimosis, small nose with hypoplastic alae nasi and coloboma, H-shaped cutaneous dimpling of the chin, ulnar deviation of hands with cortical thumbs and flexion of fingers, equinovarus position of feet with vertical talus and contracted toes, kyphosis, and scoliosis. Our cases do not show the typical H-shaped dimpling or the hypoplastic alae nasi, and the joint involvement including elbows, hips, and knees in our cases is far more extensive than noted in Freeman-Sheldon syndrome.

Blepharophimosis is a characteristic finding of the blepharophimosis-ptosis-epicanthus inversus syndrome, which has been classified in two clinical types and was shown to be a genetically heterogeneous disorder [Warburg et al., 1995]. In type 1 there is reduced female fertility; hence this is an unlikely syndrome to affect mother and son. Type 2 is not associated with decreased fertility, but this syndrome can not account for

other manifestations seen in our cases, e.g., congenital contractures or mask-like face. In both patients no history of environmental teratogen exposure was obtained, specifically no exposure to ethanol or valproic acid. No evidence of prenatal infection was found in patient 2.

After excluding many of the known syndromes associated with multiple congenital contractures in our patients we think that these two cases most closely resemble the three patients described by Hall et al. [1982] as distal arthrogryposis type IIb. This autosomal dominant condition is characterized by shortness of stature, short neck, ptosis, immobile facial expression, decreased ocular range of motion, poorly formed and large anteverted ears, and smooth fingers with camptodactyly. Our patients have blepharophimosis rather than ptosis and their extraocular movements are intact; their ears are neither poorly formed nor large or anteverted. In spite of these differences the similarity of facial expression is striking, as are those of the hands with camptodactyly and absent flexion creases of the fingers. Short stature and short neck was also seen in all patients. Distal arthrogryposis type IIa (Gordon syndrome) presents with clubfoot deformity, mild hip involvement, and camptodactyly in adults, and about 50% of patients have short stature, ptosis, and cleft palate [Hall et al., 1982]. Although F.J. had a cleft palate, our patients do not exactly fit this description, because they have more significant involvement of proximal joints and limited facial expression.

Lai et al. [1991] documented a father and his son with congenital limb contractures involving distal and proximal joints, limited ocular movements, electroretinal abnormalities, and somewhat immobile face. They did not have short stature or short neck. These patients shared some findings with those previously reported by Hall et al. [1982], but they were considered to have a different syndrome. An autosomal-dominant syndrome of distal arthrogryposis with absent digital flexion creases and sensori-neural deafness was described in a single family [Stewart and Bergstrom, 1971]; none of the patients had proximal joint involvement or ophthalmoplegia.

Since there is overlap of the manifestations in our cases and those described previously in several different distal arthrogryposis syndromes, these patients may have the same autosomal dominant condition with variable interfamilial expression. Further delineation of the full spectrum will be possible through documentation of more families with distal arthrogryposis and additional findings.

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